

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Assistant Commissioner for Patents
United States Patent and Trademark
Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

| | |
|---|---|
| Date of mailing (day/month/year) 06 April 2000 (06.04.00) | |
| International application No. PCT/EP99/06217 | Applicant's or agent's file reference PG3553 |
| International filing date (day/month/year) 25 August 1999 (25.08.99) | Priority date (day/month/year) 26 August 1998 (26.08.98) |
| Applicant CHARO, Jehad et al | |

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

17 February 2000 (17.02.00)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

| | |
|---|----------------------------------|
| The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland | Authorized officer C. Villet |
| Facsimile No.: (41-22) 740.14.35 | Telephone No.: (41-22) 338.83.38 |

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|--|
| Applicant's or agent's file reference PG3553 | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/EP 99/06217 | International filing date (day/month/year) 25/08/1999 | (Earliest) Priority Date (day/month/year) 26/08/1998 |
| Applicant GLAXO GROUP LIMITED et. al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

METHOD OF DNA VACCINATION

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 1-13 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

T/EP 99/06217

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K39/00 A61K39/39 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| X | WO 94 07479 A (WELLCOME FOUND ; RHODES JOHN RICHARD (GB)) 14 April 1994 (1994-04-14) cited in the application the whole document --- | 18-22 |
| A | RHODES J ET AL: "Therapeutic potentiation of the immune system by costimulatory Schiff-base-forming drugs 'see comments!.' NATURE, (1995 SEP 7) 377 (6544) 71-5. , XP002128171 cited in the application the whole document --- -/-- | 1-24 |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

19 January 2000

Date of mailing of the international search report

04/02/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fernandez y Branas, F

International Application No

T/EP 99/06217

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | <p>RHODES J. ET AL: "Covalent chemical events in immune induction: fundamental and therapeutic aspects" IMMUNOLOGY TODAY, vol. 17, no. 9, 1996, pages 436-441, XP002128172 the whole document ---</p> | 1-24 |
| A | <p>SASAKI S. ET AL: "Comparison of intranasal and intramuscular immunization against human immunodeficiency virus type 1 with a dna-monophosphoryl lipid A adjuvant vaccine" INFECTION AND IMMUNITY, vol. 66, no. 2, February 1998 (1998-02), pages 823-826, XP002128173 the whole document ---</p> | 1-24 |
| A | <p>SASAKI S. ET AL: "Adjuvant effect of Ubenimex on a DNA vaccine for HIV-1" CLINICAL AND EXPERIMENTAL IMMUNOLOGY , vol. 111, January 1998 (1998-01), pages 30-35, XP000867267 the whole document -----</p> | 1-24 |

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

T/EP 99/06217

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| WO 9407479 A | 14-04-1994 | AT 146075 T | 15-12-1996 |
| | | AU 676491 B | 13-03-1997 |
| | | AU 4831193 A | 26-04-1994 |
| | | CA 2124677 A | 14-04-1994 |
| | | CN 1091005 A | 24-08-1994 |
| | | CZ 9401327 A | 15-02-1995 |
| | | DE 69306545 D | 23-01-1997 |
| | | DE 69306545 T | 03-04-1997 |
| | | DK 609606 T | 17-03-1997 |
| | | EP 0609606 A | 10-08-1994 |
| | | EP 0614357 A | 14-09-1994 |
| | | EP 0678298 A | 25-10-1995 |
| | | ES 2096215 T | 01-03-1997 |
| | | GR 3022541 T | 31-05-1997 |
| | | HR 931243 A | 31-12-1995 |
| | | HU 70482 A | 30-10-1995 |
| | | JP 7002660 A | 06-01-1995 |
| | | JP 7504204 T | 11-05-1995 |
| | | MX 9306079 A | 30-06-1994 |
| | | NZ 256110 A | 27-07-1997 |
| | | SG 48993 A | 18-05-1998 |
| | | SI 9300514 A | 30-06-1994 |
| | | SK 65294 A | 08-03-1995 |
| | | US 5508310 A | 16-04-1996 |
| | | US 5872151 A | 16-02-1999 |
| | | ZA 9307286 A | 30-06-1995 |

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International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| (51) International Patent Classification ⁷ : A61K 39/00, 39/39, 48/00 | A1 | (11) International Publication Number: WO 00/12121 (43) International Publication Date: 9 March 2000 (09.03.00) |
| (21) International Application Number: <u>PCT/EP99/06217</u> (22) International Filing Date: 25 August 1999 (25.08.99) (30) Priority Data: 9818627.3 26 August 1998 (26.08.98) GB (71) Applicant (for all designated States except US): GLAXO GROUP LIMITED [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): CHARO, Jehad [SY/SE]; Cancer Centre Karolinska, Karolinska Hospital, S-171 76 Stockholm (SE). KIESSLING, Rolf [SE/SE]; Cancer Centre Karolinska, Karolinska Hospital, S-171 76 Stockholm (SE). (74) Agent: STOTT, Michael, J.; Glaxo Wellcome plc, Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB). | | (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> |
| (54) Title: METHOD OF DNA VACCINATION | | |
| (57) Abstract | | |
| <p>A method of vaccinating a mammal against a disease state, comprising administering to said mammal, within an appropriate vector, a nucleotide sequence encoding an antigenic peptide associated with the disease state; additionally administering to said mammal a compound which enhances both humoral and cellular immune responses initiated by the antigenic peptide, the compound being selected from the list contained herein, wherein the compound is preferably Tucaresol or a physiologically acceptable salt or ester thereof, where appropriate.</p> | | |

FOR THE PURPOSES OF INFORMATION ONLY

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REC'D 17 JAN 2001

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

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|---|---|--|
| Applicant's or agent's file reference PG3553/WO | FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) | |
| International application No. PCT/EP99/06217 | International filing date (day/month/year) 25/08/1999 | Priority date (day/month/year) 26/08/1998 |
| International Patent Classification (IPC) or national classification and IPC A61K39/00 | | |
| Applicant GLAXO GROUP LIMITED et. al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 17/02/2000 | Date of completion of this report 11.01.2001 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016 | Authorized officer Fernandez y Branas,F Telephone No. +31 70 340 2774  |

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/06217

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-38 as originally filed

Claims, No.:

1-24 as originally filed

Drawings, sheets:

1-9 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
- ☒ claims Nos. 1-13 with respect to Industrial Applicability.

because:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/06217

- ☒ the said international application, or the said claims Nos. 1-13 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|-------------------------------|------|--------|-------------|
| Novelty (N) | Yes: | Claims | 1-17, 23-24 |
| | No: | Claims | 18-22 |
| Inventive step (IS) | Yes: | Claims | 1-17, 23-24 |
| | No: | Claims | 18-22 |
| Industrial applicability (IA) | Yes: | Claims | 14-24 |
| | No: | Claims | |

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/06217

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-13 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1.....WO-A-9407479 (THE WELLCOME FOUNDATION LIMITED)

For the assessment of the present claims 1-24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/EP99/06217

D1 discloses the use of the compounds of the present application, capable of forming schiff bases or hydrazones with T-cell surface carbonyl or amino groups, for stimulating and potentiating immune responses, including the use of said compounds (e.g. tucaresol) in vaccine formulations as adjuvants, see page 17 third paragraph.

Claims 18-22 are directed to the use of said compounds in the manufacture of a medicament wherein the administration of said compound to a mammal enhances both humoral and cellular responses initiated by an antigenic peptide associated with a disease. The subsequent statement in claim 18, "peptide being expressed as a result of administration to said mammal of a nucleotide sequence encoding for the peptide" is not limitative and does not restrict the scope of the claim. As a result claims 18-22 can be regarded as claiming the second medical use of said compounds for enhancing the humoral and cellular immune response to a disease antigenic peptide. This is precisely the same subject matter as the teaching disclosed in D1.

It is only in claim 23 that it is mentioned that the medicament further comprises the nucleotide sequence.

Thus, the subject matter of claims 18-22 lacks novelty in the sense of Article 33(2) PCT.

The subject matter of claims 1-17 and 23-24 appear to be new in the sense of Article 33(2) PCT

D1 is considered the closest prior art. The difference between D1 and the present application is that in the present application a DNA vaccine is used in combination with one of the compounds specified in claim 1 in order to obtain an increased cellular and humoral immune response to the antigen expressed by said DNA. In view of this difference the problem solved by the present application can be defined as the provision of alternative vaccines.

Although DNA vaccines in combination with adjuvants or immunostimulatory compounds are known in the state of the art, the IPEA sees no suggestion in the prior art that would have directed the skilled person to the subject matter claimed in the present application, see also the results obtained as exemplified in figures 4, 6 and 7 of the present application.

Thus, the subject matter of the claims 1-17 and 23-24 involves an inventive step in the sense of Article 33(3) PCT.

Re Item VIII

Certain observations on the international application

For the reasons given above in item V, the subject matter of claim 18 is unclear in the sense of Article 6.

Claim 24 is equally unclear, as it does not state that the compounds are the compounds of claim 1.

The applicant has only given technical support for the compound first mentioned in the claims (tucaresol, 4-(2-formyl-3-hydroxyphenoxy)methyl) benzoic acid). Whether the rest of the compounds would function in the claimed manner is purely speculative. Thus, the subject matter of claims 1-12, 14-16, 18-20 and 22-24 lacks technical support in the sense of Article 6 PCT.